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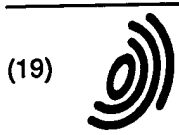
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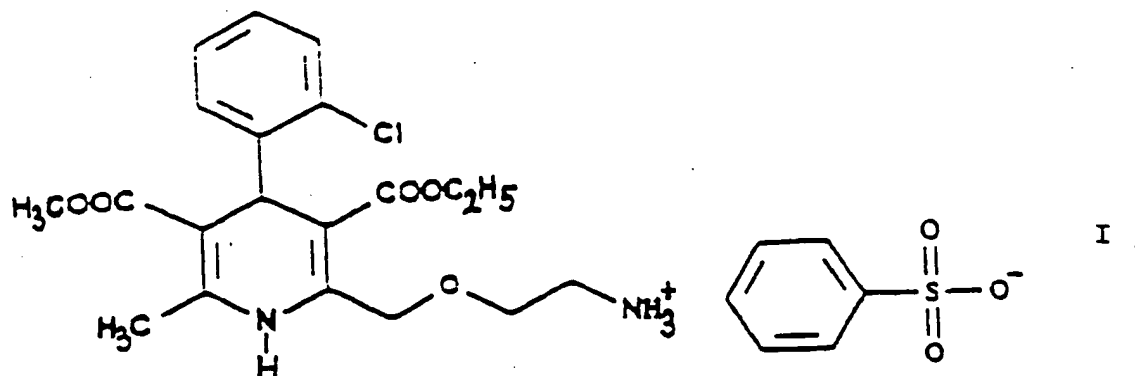
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(54) A process and intermediate compounds for the preparation of amlodipine benzene sulphonate

(57) A subject matter of the invention is a process for preparing 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4--[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt of Formula



in which 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] hexaminium iodide of Formula

Description

[0001] The present invention is concerned with a new process and new intermediates for preparing 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt. This compound is a known pharmaceutically active ingredient having the INN amlodipine besylate.

[0002] Amlodipine besylate is a calcium antagonist of the dihydropyridine-dicarboxylate type and possesses valuable strong long-lasting blood pressure decreasing and antianginal properties.

[0003] According to the known processes the dihydropyridine structure of amlodipine is built up by means of the Hantzsch synthesis suggested by the Prior Art for reactions of this type. The main feature of the process disclosed in EP 89,167 and HU 186,868 is that the primary amino group is formed in the last step of the synthesis either by removing the protecting group from a protected amino group or by reducing the corresponding azide. The protected amino group or the azido group is introduced into the molecule by incorporating into the acetoacetate component of the Hantzsch synthesis.

[0004] According to the first process mentioned above in the Hantzsch synthesis a 4-[2'-(amino)-ethoxy]-acetoacetic ester bearing a protected amino group, 2-[chloro]-benzaldehyde and an amino crotonic acid ester were reacted, or in a variant of said process a 4-[2'-(amino)-ethoxy]-acetoacetic ester was condensed first with a 2-[chloro]-benzaldehyde and the "ylidine" derivative thus obtained was reacted with an amino crotonic acid ester. Amlodipine was prepared by removing the protecting group from the dihydropyridine derivative containing a protected primary amino group obtained in the Hantzsch synthesis.

[0005] According to the other process referred to Hantzsch synthesis it was performed by reacting a 4-[2'-(azido)-ethoxy]-acetoacetic acid ester, 2-chloro-benzaldehyde and amino crotonic acid ester. The primary amino group of amlodipine was formed by reducing the azido group.

[0006] In the EP 89,167 cited above pharmaceutically acceptable acid addition salts of amlodipine were disclosed. Said salts were prepared from amlodipine by salt formation. Among the salts the maleate has been described as the most advantageous one.

[0007] The disadvantage of the above processes is the relatively low yield of the individual reaction steps (the yield of the Hantzsch synthesis has not been even disclosed). It is known furtheron that the azide is explosive (see citation C.A. 105, 11321t relating to the relevant azido compound).

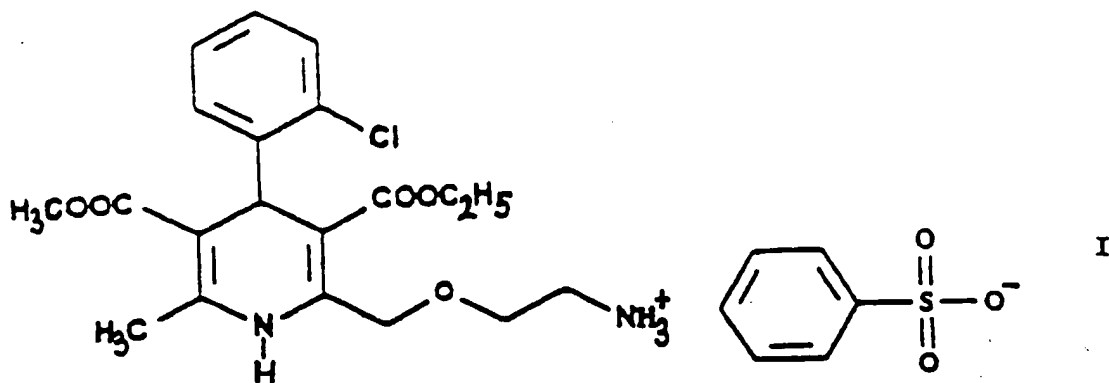
[0008] In DE 3,710,457 the benzenesulfonic acid salt of amlodipine and a process for preparing it have been disclosed. According to this patent said salt exhibits numerous advantages over other known salts of amlodipine, particularly in the incorporation of the salt into pharmaceutical compositions. Amlodipine besylate was prepared by reacting amlodipine base with a solution of benzenesulfonic acid or the ammonium salt thereof formed with an inert solvent and isolating the amlodipine besylate thus obtained from the reaction mixture.

[0009] In EP 599,220 a further process for preparing amlodipine besylate has been disclosed. An amlodipine derivative containing a trityl protective group on the primary amino group was prepared by using the conventional Hantzsch synthesis. The protecting trityl group was removed by hydrolysis carried out in the presence of benzenesulfonic acid. Thus amlodipine besylate is obtained without isolating the amlodipine base. The significant drawback of this process resides in the low yield. It is a further important disadvantage that pure end-product can only be obtained with the aid of extremely complicated measures. The overall yield is only 7%, related to 2-[chloro]-benzaldehyde.

[0010] The problem underlying to the invention is to provide for a new process and new intermediates for preparing 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt (amlodipine besylate) by which by overcoming the above disadvantages of the known processes this compound can be obtained with high yields and in a simple way and with elimination of the isolation of amlodipine base.

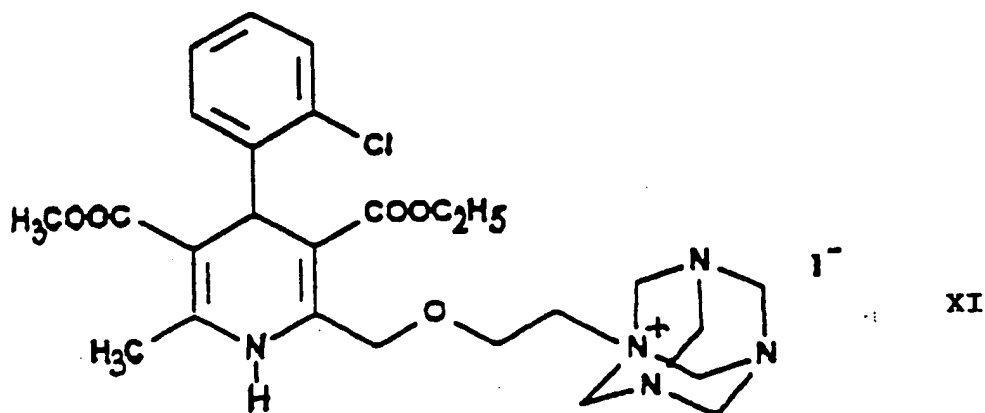
[0011] Surprisingly this has been achieved by the present invention.

[0012] A subject matter of the invention is a process for preparing 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt of Formula

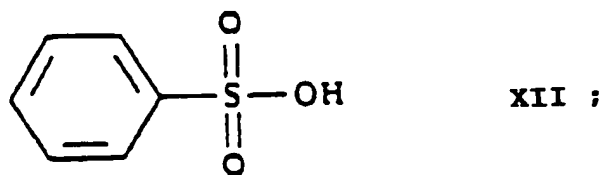


including its optically active isomers, which is characterized by

a₁) reacting 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula

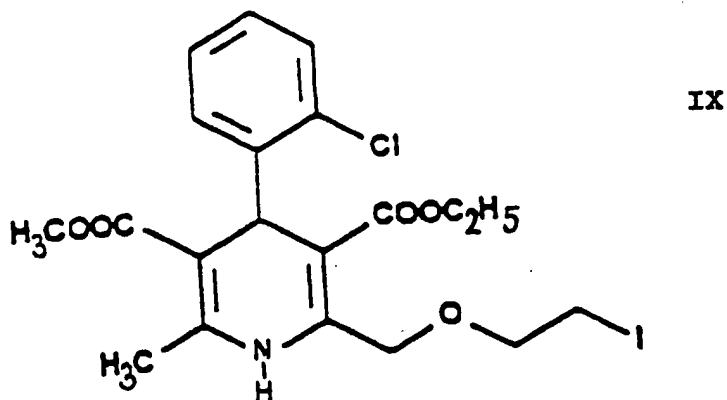


with benzenesulfonic acid of Formula

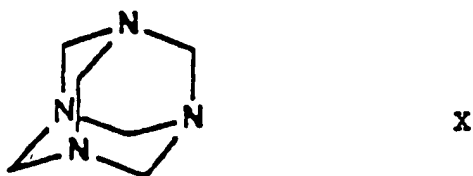


or

a₂) reacting 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula

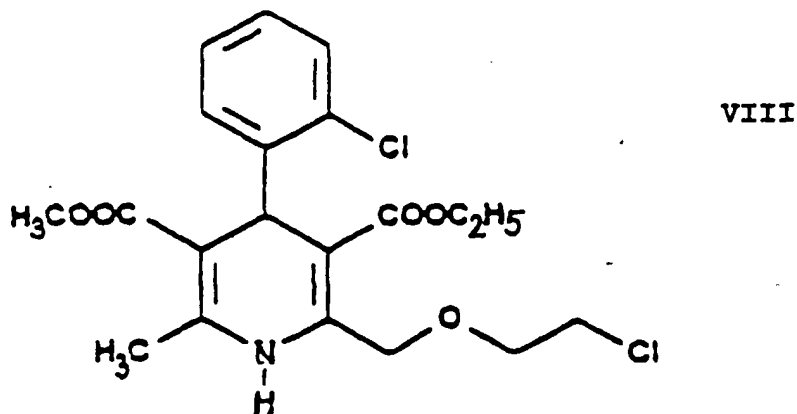


with hexamethylene tetramine of Formula



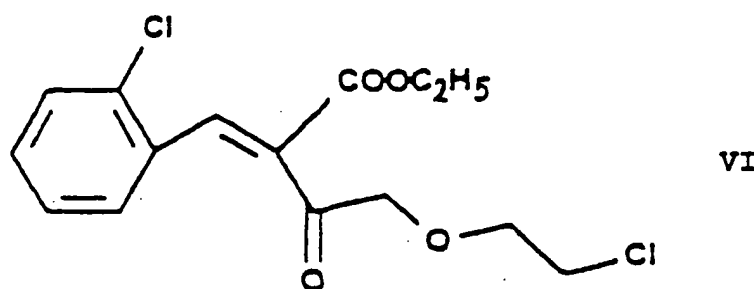
30 and reacting the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexamini-um iodide of Formula XI thus obtained with benzenesulfonic acid of Formula XII;

or
a₃) exchanging in 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula



50 the chlorine for iodine, reacting the 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX thus obtained with hexamethylene tetramine of Formula X and reacting the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexamini-um iodide of Formula XI thus obtained with benzenesulfonic acid of Formula XII;

55 or
a₄) reacting ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula



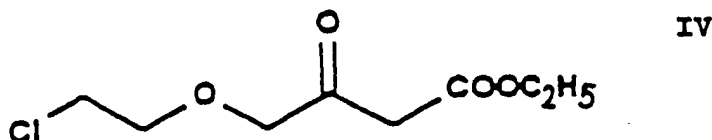
with methyl-3-(amino)-crotonate of Formula



exchanging in the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII thus obtained the chlorine for iodine, reacting the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX thus obtained with hexamethylene tetramine of Formula X and reacting the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI thus obtained with benzenesulfonic acid of Formula XII;

or

a₅) reacting ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula



with 2-(chloro)-benzaldehyde of Formula

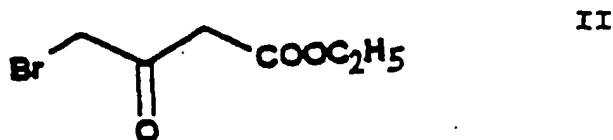


reacting the ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI thus obtained with methyl-3-(amino)-crotonate of Formula VII, exchanging in the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII thus obtained the chlorine for iodine reacting the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula X thus obtained with hexamethylene tetramine of Formula X and

reacting the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI thus obtained with benzenesulfonic acid of Formula XII;

or

a₆) reacting ethyl-4-(bromo)-acetoacetate of Formula



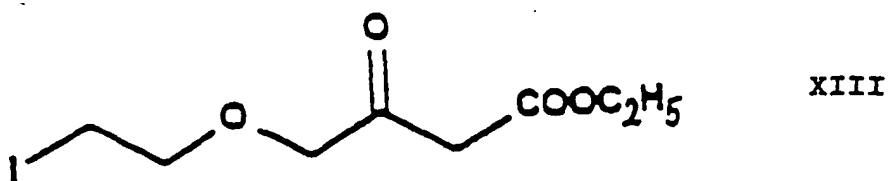
with ethylene chlorohydrine of Formula



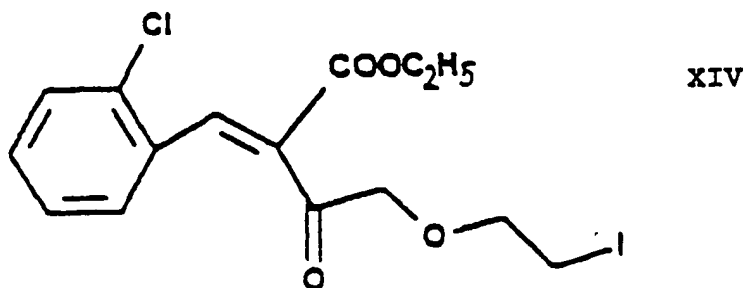
reacting the ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV thus obtained with 2-(chloro)-benzaldehyde of Formula V, reacting the ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI thus obtained with methyl-3-(amino)-crotonate of Formula VII, exchanging in the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII thus obtained the chlorine for iodine, reacting the 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX thus obtained with hexamethylene tetramine of Formula X and reacting the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI thus obtained with benzenesulfonic acid of Formula XII;

or

a₇) exchanging in the ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV the chlorine for iodine, reacting the ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate of Formula



thus obtained with 2-(chloro)-benzaldehyde of Formula V, reacting the ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula



thus obtained with methyl-3-(amino)-crotonate of Formula VII, reacting the 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX thus obtained with hexamethylene tetramine of Formula X and reacting the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI thus obtained with benzenesulfonic acid of Formula XII,

in variants a₅) and a₆) alternatively reacting the ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV with the 2-(chloro)-benzaldehyde of Formula V and the methyl-3-(amino)-crotonate of Formula VII to the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII without isolating the ethyl-4-[2'-(chloro)-ethoxy]-2-[2'-(chloro)-benzylidene]-acetoacetate of Formula VI,

optionally separating optically active isomers in a manner known per se from the 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt of Formula I, the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII, the 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX or the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI thus obtained and further reacting the optically active isomers of the last three ones thus obtained.

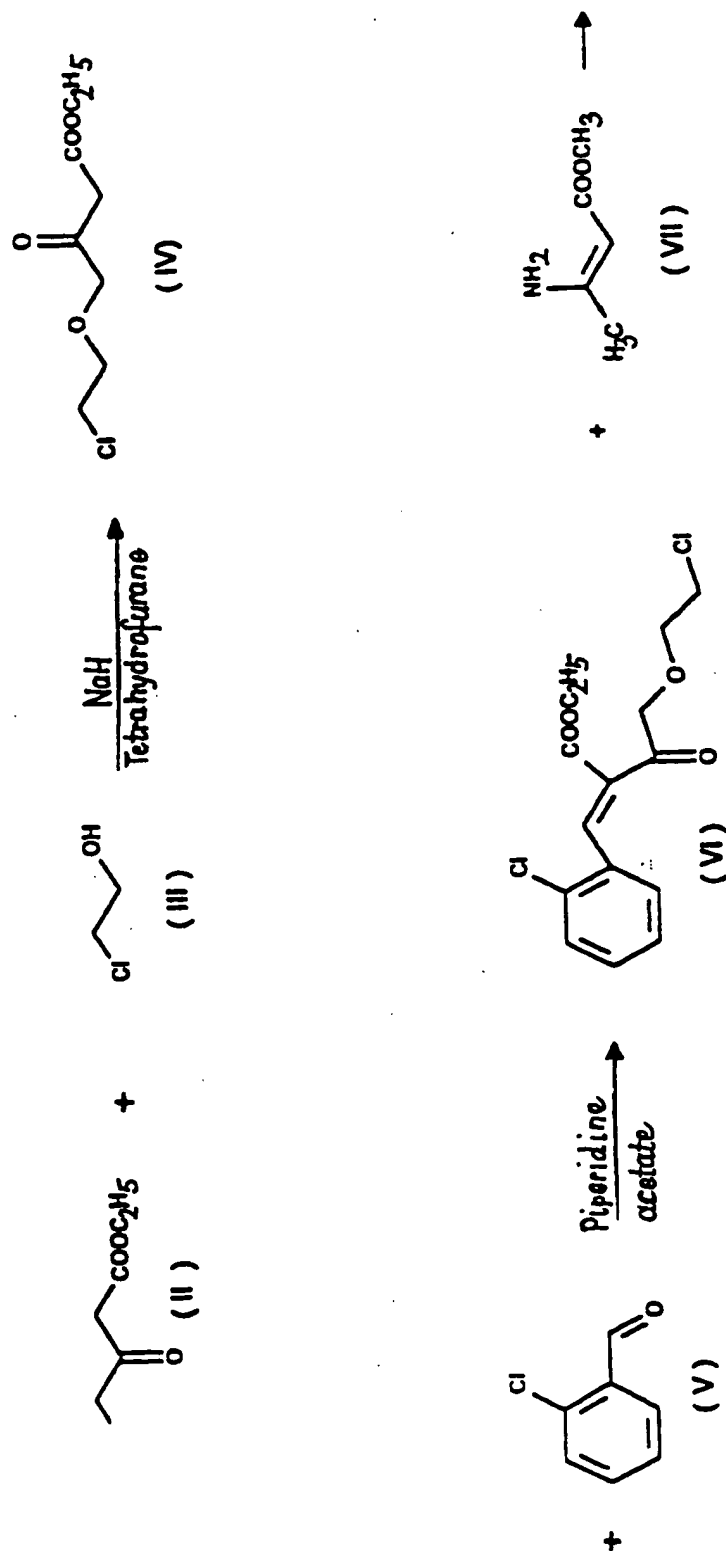
[0013] The essential feature of the present invention is that in the Hantzsch synthesis it is the benzylidene derivative ethyl-4-[2'-(chloro)-ethoxy]-2-[2'-(chloro)-benzylidene]-acetoacetate of Formula VI prepared from ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV and 2-(chloro)-benzaldehyde of Formula V which is reacted with the amino crotonic acid ester methyl-3-(amino)-crotonate of Formula VII whereby the new 2-(chloroethoxy)-dihydropyridine derivative 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII and after chlorine→iodine exchange the new 2-(iodoethoxy)-dihydropyridine derivative 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX are obtained with good yields.

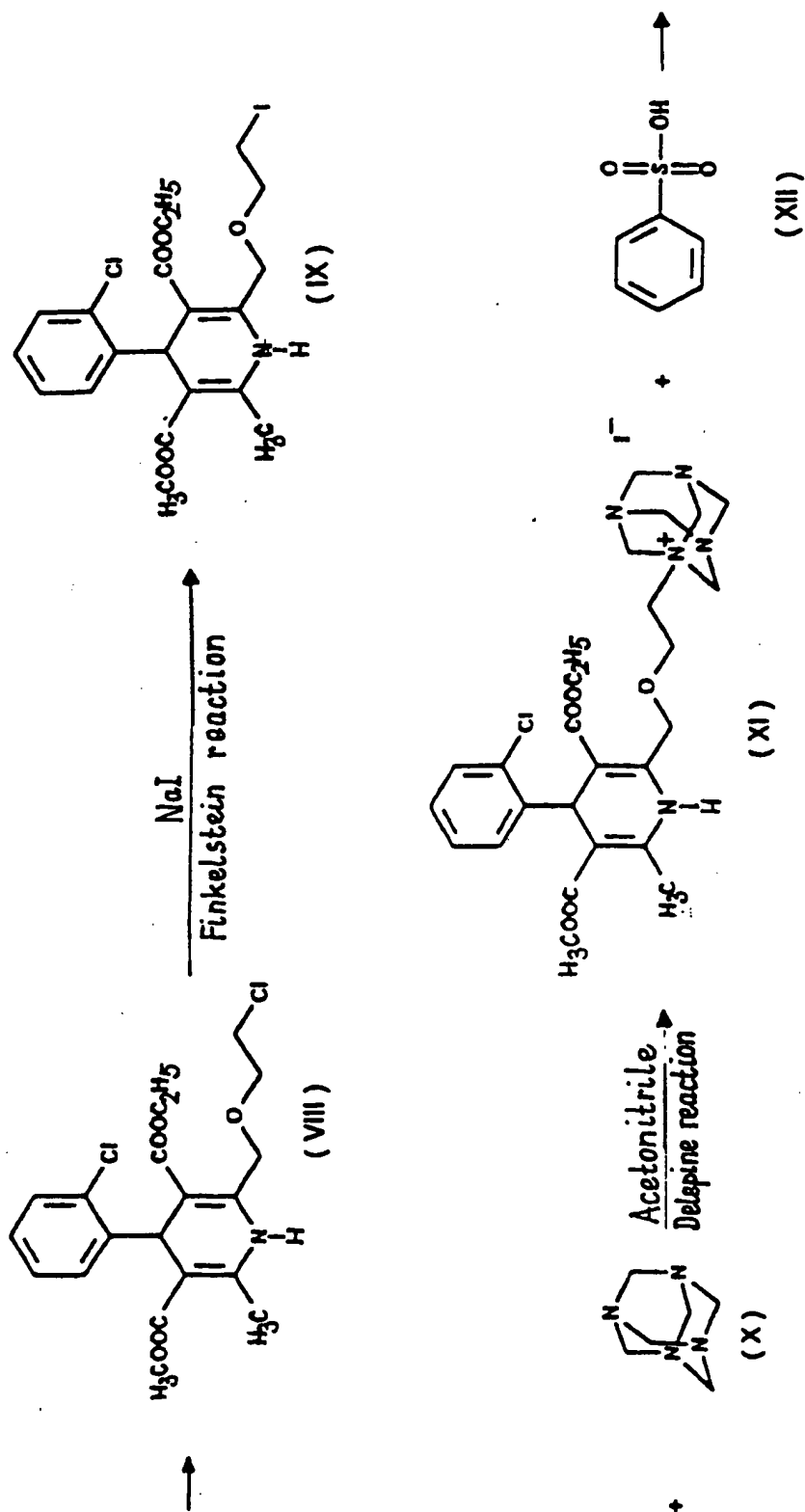
[0014] The compounds 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] and 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formulae VIII and IX, respectively, are new, not described in the Prior Art. In this way 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt (amlodipine besylate) is prepared by a new and very advantageous method by ammonolysis of the halogeno derivative 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX by means of the so-called Delapine reaction. The halogen iodine is ultimately replaced by the amino group by using hexamethylene tetramine as ammonia source and converted into an iodide anion. The urotropine salt 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI formed is decomposed by using benzenesulfonic acid whereby 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2'-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt (amlodipine besylate) of Formula I is directly isolated from the reaction mixture. Also the latter process is new, not disclosed in the Prior Art.

[0015] According to the process of the present invention - contrary to methods described in the Prior Art - the primary amino group is not built up by introducing it into the molecule as a part of the acetoacetic acid ester component in protected form and subsequently removing the protecting group of the amino group but rather by a halogen→amine exchange reaction carried out after the Hantzsch reaction performed by using the corresponding halogeno compound. According to a characteristic essential element of the process of the present invention the latter reaction is carried out in a manner not disclosed in the Prior Art whereby in the reaction not amlodipine base but directly the desired besylate

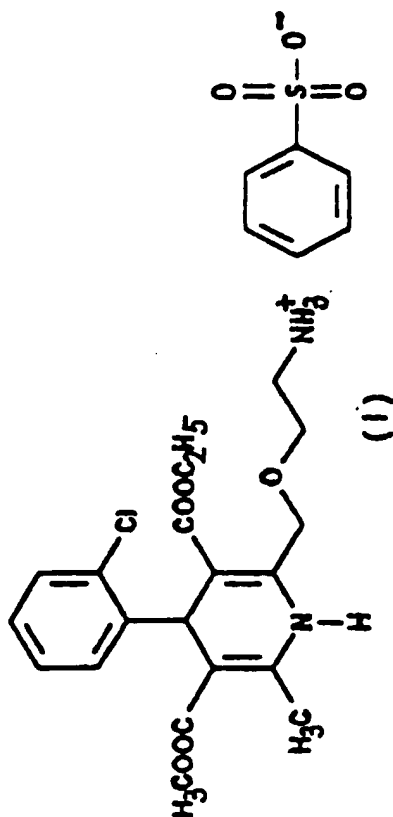
salt 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt is formed. The process is shown on the following reaction scheme.

REACTION SCHEME



REACTION SCHEME
continued

REACTION SCHEME
continued



[0016] The reaction of the process of the present invention in which ethylene chlorohydrine [2-(chloro)-ethanol] of Formula III is O-alkylated with ethyl-4-(bromo)-acetoacetate of Formula II results in the new compound ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV. The reaction can be carried out in a known manner. The reaction can be performed in an inert solvent, preferably 1 or more aliphatic and/or alicyclic ether(s), particularly tetrahydrofuran, at a temperature of about -10°C or below this temperature. Advantageously the hydrogen bromide formed is bound with a basic substance, preferably with sodium hydride, which can be used in the form of an oily suspension or can be made previously free of paraffine. The reaction mixture may be worked up in a known manner by decomposing with an acid, neutralization and extraction. The pure product may be obtained by fractionated distillation *in vacuo*.

[0017] As reaction product of the aldol condensation of the chloroethoxy-acetoacetic acid ester ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV with 2-(chloro)-benzaldehyde of Formula V the "ylidene" derivative ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI is obtained. Preferably this reaction is carried out in the presence of piperidine acetate as catalyst, advantageously in a catalytic amount of the latter, whereby the ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI is obtained in very high yield. The piperidine acetate catalyst is preferably used in a 0.01 to 0.1 molar amount, related to 1 mole of the ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV. As reaction medium advantageously 1 or more protic solvent(s) may be used, preferably 1 or more alkanol(s), particularly isopropanol. Advantageously as reaction temperatures from 10°C to 60°C are

applied, one may preferably work at room temperature. The reaction time can be varied from 5 to 15 hours and preferably 10 hours are chosen. The reaction mixture may be worked up by evaporating the solvent and washing with water. The crude product ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI thus obtained is generally suitable for further chemical transformation.

[0018] One may also proceed by subjecting the ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI to further chemical reaction directly, without isolation, in the solvent used.

[0019] In the preparation of the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII by Hantzsch synthesis the ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI is reacted with methyl-3-(amino)-crotonate of Formula VII one may advantageously proceed by heating to boiling the said reactants. Furthermore it is advantageous to carry out this reaction in an organic solvent. Preferably the reaction of the ethyl-4-[2'-(chloro)ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI with the methyl-3-(amino)-crotonate of Formula VII is carried out in 1 or more C₁₋₄-alkanol(s), particularly methanol, ethanol and/or isopropanol, and/or polar aprotic organic solvent(s), particularly acetonitrile.

[0020] One may also proceed by reacting 2-(chloro)-benzaldehyde of Formula V, the keto ester ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV and the amino crotonate methyl-3-(amino)-crotonate of Formula VII without isolating the benzylidene derivative ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI until the reaction becomes complete. As reaction time advantageously from 15 to 20 hours or shorter are chosen. The reaction mixture can be worked up in a known manner, e.g. by cooling and filtration.

[0021] The reaction of exchanging in the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII the chlorine for iodine to result in the 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX is the "Finkelstein reaction" known from the Prior Art *per se*. This reaction is preferably carried out by reacting the 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII with 1 or more alkali iodide(s), particularly sodium iodide. According to the teaching of the Prior Art this reaction is carried out preferably in acetone in view of the solubility conditions. The process of the present invention may be performed in acetone but the use of 1 or more alkanol(s) having a high boiling point, particularly isopropanol, proved to be particularly advantageous. The reaction may be carried out under heating, preferably at the boiling point of the reaction mixture. The reaction time is chosen generally from 20 to 25 hours or shorter. The reaction mixture may be worked up in a known manner, e.g. by filtration after intensive cooling. The dihydropyridine derivative 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX is obtained with good yields.

[0022] According to an alternative embodiment of the process of the present invention the chlorine-iodine exchange is carried out at the stage of the chloroethoxy acetoacetate ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV. This reaction gives the iodo-acetoacetate ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate of Formula XIII. The reaction is preferably carried out in acetone as medium at the boiling point of the reaction mixture. Furthermore preferably this chlorine-iodine exchange is carried out by reacting the ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV with 1 or more alkali iodide(s), particularly sodium iodide. The product may be purified by fractionated distillation. The reaction of the ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate of Formula XIII thus obtained with the 2-(chloro)-benzaldehyde of Formula V to yield the benzylidene derivative ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula XIV is advantageously carried out as described in connection with the reaction of the ethyl-4-[2'-(chloro)ethoxy]-acetoacetate of Formula IV with the 2-(chloro)benzaldehyde of Formula V. The reaction of the ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula XIV thus obtained with the methyl-3-(amino)-crotonate of Formula VII to yield the iodoethoxy-dihydropyridine derivative 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX is advantageously carried out in a manner analogous to the Hantzsch reaction of the ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI with the methyl-3-(amino)-crotonate of Formula VII.

[0023] The reaction of the iodo derivative 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX - this being more reactive than the chloroethoxy-dihydropyridine 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII - with hexamethylene tetramine (urotropine) of Formula X is the formation of a quaternary salt, namely 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI. According to the teaching of the Prior Art salts of such type are generally prepared in apolar-protic solvents. However, it has been found, that the said reaction of the process according to the invention may be carried out more advantageously by using 1 or more C₁₋₅-alkanol(s), e.g. methanol, ethanol and/or isopropanol, and/or acetonitrile as reaction medium. One may work particularly preferably in acetonitrile as medium. The reactants may be used in equimolar amount, but hexamethylene tetramine (urotropine) of Formula X may also be used preferably in an excess of 10 to 15%. The reaction may be carried out advantageously at temperatures from room temperature to the boiling point of the solvent, preferably at 40 to 55°C, particularly 45 to 50°C. One

may proceed by adding the reaction components simultaneously to the solvent or adding the iodo compound 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX to the solution of hexamethylene tetramine, preferably in small portions. As reaction time advantageously 20 to 50 hours, preferably 30 to 40 hours, are chosen. The dihydropyridine-urotropine quaternary salt 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI precipitates as a solid and can be simply filtered off at room temperature. The crude product is of a purity suitable for the preparation of the end-product and no further purification is required.

[0024] The reaction of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid of Formula XII to yield 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt (amlodipine besylate) is a hydrolysis.

[0025] Advantageously the hydrolysis of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid of Formula XII is carried out in a mixture of water and 1 or more organic solvent(s). According to one alternative 1 or more water miscible organic solvent(s) is/are used as [an] organic solvent(s) for the hydrolysis of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid of Formula XII. Preferably 1 or more straight or branched chained C₁₋₃-alkanol(s), e.g. methanol, ethanol and/or isopropanol, is/are used as [a] water miscible solvent(s) for the hydrolysis of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid of Formula XII.

[0026] According to another alternative 1 or more organic solvent(s) partially miscible or immiscible with water is/are used as [an] organic solvent(s) for the hydrolysis of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid of Formula XII. In this alternative preferably 1 or more C₄₋₈-alkanol(s), particularly n-butanol, and/or ethyl acetate is/are used as [an] organic solvent(s) for the hydrolysis of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid of Formula XII. The reaction may be carried out advantageously at temperatures from room temperature to the boiling point of the solvent; one may preferably work at the boiling point of the reaction mixture. Preferably benzenesulfonic acid of Formula XII is used in at least a 4 molar amount, related to 1 mole of the 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI. For practical reasons it is preferred to use not more than 10 molar equivalents of benzenesulfonic acid of Formula XII. According to a particularly preferred embodiment of the process the reaction is carried out by using about 5 molar equivalents of benzenesulfonic acid of Formula XII. The reaction mixture may be worked up in a manner known *per se*.

[0027] The starting materials ethylene chlorohydrine of Formula III, 2-(chloro)-benzaldehyde of Formula V, hexamethylene tetramine of Formula X and benzenesulfonic acid of Formula XII are commercially available. The ethyl-4-(bromo)-acetoacetate of Formula II is a known compound and can be prepared e.g. according to US 3,786,082 and EP 102,893. The methyl-3-(amino)-crotonate of Formula VII has been known as well (HU 202,474).

[0028] The intermediates ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV, ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI, 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy]-methyl-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII, 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy]-methyl-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX, 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI, ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate of Formula XIII and ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula XIV are new compounds, not disclosed in the Prior Art.

[0029] Hence a further subject matter of the present invention are the new compounds ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate of Formula IV, ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula VI, 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy]-methyl-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII, 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy]-methyl-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX, 3-[ethyl]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI, ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate of Formula XIII and ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate of Formula XIV which are valuable intermediates via which the end product 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt (amlodipine besylate) can be prepared by a process having originality in a superior way.

[0030] These intermediates can be prepared by stopping the respective variants of the process according to the invention at the suitable stage.

[0031] Compounds of the dihydropyridine dicarboxylate structure are mixed esters and contain an asymmetrical center. Such compounds may occur in the form of a pair of enantiomers, which can be separated by methods well-

known from the Prior Art. The present invention also encompasses the preparation of the individual isomers (dextro and laevo rotatory isomers) and mixtures thereof (including racemic mixtures), namely of 3-[ethyl]-5-[methyl]-2-[2'-(aminoethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-methyl-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] benzenesulfonic acid salt {amlodipine besylate} of Formula I, 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy]-methyl-4-[2''-(chloro)-phenyl]-6-methyl-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula VIII, 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy]-methyl-4-[2''-(chloro)-phenyl]-6-methyl-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] of Formula IX and 3-[ethyl]-5-[methyl]-2-[2'-(yl-ethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-methyl-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI.

[0032] Also the hydrolysis of the quaternary salt 3-[ethyl]-5-[methyl]-2-[2'-(yl-ethoxy)-methyl]-4-[2''-(chloro)-phenyl]-6-methyl-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide of Formula XI with benzenesulfonic acid is a new process having originality.

[0033] The main advantage of the present invention is that the yields of the individual steps are high. Thus also the yield of the Hantzsch cyclisation step used in the process according to the invention is higher than that of the known cyclisation reactions leading to amlodipine. A further advantage of the invention resides in the fact that there is no need to isolate the amlodipine base because the precipitated salt is directly formed in one step. The process is feasible on industrial scale too, no special equipment being required.

[0034] Further details of the present invention are to be found in the following Examples.

Example 1

Ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate (IV)

[0035] 10.38 g (0.25 mole) of a 57.8% by weight paraffine only suspension of sodium hydride are added to 110 ml of tetrahydrofurane. The mixture is cooled to a temperature of from -10°C to -20°C whereupon at this temperature 10.08 g (0.125 mole) of ethylene chlorohydrine (III) are added under nitrogen dropwise. The mixture is stirred for 20 minutes, whereupon at the same temperature a solution of 26.18 g (0.125 mole) of ethyl-4-(bromo)-acetoacetate (II) and 35 ml of tetrahydrofurane is added. The reaction mixture is stirred for 20 minutes, allowed to warm to room temperature, kept at this temperature for 6 hours, poured into 270 ml of 1 N hydrochloric acid under cooling and extracted with dichloro methane. The organic layer is dried and evaporated. The residual oil is made free of paraffine by treatment with a mixture of acetonitrile and benzene in a ratio by volume of 1 : 1. The product is distilled off in vacuo. Thus 17.47 g of the desired compound are obtained, yield 67%, bp.: 110°C/2 Hg mm.

Elementary analysis: for the Formula $C_8H_{13}ClO_4$ (208,41):

calculated:	C 46.05%,	H 6.28%,	Cl 16.99%;
found:	C 46.45%,	H 6.11%,	Cl 16.52%.

Example 2

Ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate (XIII)

[0036] To a solution of 19 g (91 millimoles) of ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate (IV) and 380 ml of acetone 134.4 g (910 millimoles) of sodium iodide are added. The reaction mixture is heated to boiling for 13 hours. The inorganic substance is filtered off and the filtrate is evaporated in vacuo. The residual oil is dissolved in dichloro methane, the solution is washed with water, dried and evaporated. The crude product is subjected to fractionated distillation in vacuo. Bp.: 170°C/0.1 Hg mm. Thus 18.3 g of the desired product are obtained, yield 67%.

Elementary analysis: for the Formula $C_8H_{13}IO_4$ (300.091):

calculated:	C 32.02%,	H 4.37%;
found:	C 31.86%,	H 4.36%.

Example 3

Ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)benzylidene]-acetoacetate (VI)

[0037] 16.64 g (0,118 mole) of 2-(chloro)-benzaldehyde (V) and 24.7 g (0,118 mole) of ethyl-4-[2'-(chloro)-ethoxy]-acetoacetate (IV) are reacted in 365 ml of isopropanol in the presence of a piperidine acetate catalyst [10 g (11,8 millimoles) of piperidine + 0.7 g (11,8 millimoles) of acetic acid] at room temperature for 10 hours. The reaction mixture is evaporated, the residual oil is dissolved in dichloro methane, washed with water and dried. The organic phase is evaporated in vacuo. Thus 37.9 g of the desired product are obtained in the form of a yellow oil, yield 97%.

Elementary analysis: for the Formula $C_{15}H_{16}Cl_2O_4$ (331.203):

calculated:	C 54.39%,	H 4.87%,	Cl 21.41%;
found:	C 53.69%,	H 5.03%,	Cl 20.98%.

Example 4

Ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate (XIV)

[0038] 10 g (33 millimoles) of ethyl-4-[2'-(iodo)-ethoxy]-acetoacetate (XIII) and 4.64 g (33 millimoles) of 2-(chloro)-benzaldehyde (V) are reacted in 100 ml of isopropanol in the presence of a piperidine acetate catalyst [0.28 g (3.3 millimoles) of piperidine + 0.198 g (3.3 millimoles) of acetic acid] at room temperature for 10 hours. The reaction mixture is evaporated, the residual oil dissolved in dichloro methane, washed with water and dried. The organic phase is evaporated in vacuo. Thus 11.55 g of the desired product are obtained in the form of a reddish brown oil, yield 83%.

Elementary analysis: for the Formula $C_{15}H_{16}ClIO_4$ (422.643):

calculated:	C 42.63%,	H 3.82%,	Cl 8.39;
found:	C 43.00%,	H 4.12%,	Cl 8.13%.

Example 5

3-[Ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] (VIII)

[0039] A mixture of 36 g (0.1087 mole) of ethyl-4-[2'-(chloro)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate (VI) and 12.5 g (0.1087 mole) of methyl-3-(amino)-crotonate (VII) in 335 ml of isopropanol is reacted at the boiling point of the reaction mixture for 20 hours. The reaction mixture is cooled to a temperature of from 0°C to -5°C and allowed to stand in a refrigerator overnight. Next morning the precipitate is filtered, washed successively with cold isopropanol and diisopropyl ether. The crude product may be recrystallized from diisopropyl ether or aqueous acetic acid, if necessary. Thus 21.88 g of the desired product are obtained, yield 47%, mp.: 152 to 154°C.

Elementary analysis: for the Formula $C_{20}H_{23}Cl_2NO_5$ (428,32):

calculated:	C 56.08%,	H 5.41%,	N 3.27%,	Cl 16.56%;
found:	C 56.10%,	H 5.42%,	N 3.37%,	Cl 16.18%.

Example 6

3-[Ethy]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] (IX)

Method a)

[0040] A mixture of 16 g (37 millimoles) of 3-[ethyl]-5-[methyl]-2-[2'-(chloro)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] (VIII), 55.46 g (370 millimoles) of sodium iodide and 183 ml of isopropanol is stirred under boiling for 20 hours. The reaction mixture is cooled to a temperature of from 0°C to -5°C and stored in a refrigerator overnight. Next morning the precipitate is filtered off and washed with cold isopropanol. The crude product is recrystallized from isopropanol. Thus 16.35 g of the desired compound are obtained, yield 85%, mp.: 152 to 154°C.

Elementary analysis: for the Formula $C_{20}H_{23}ClINO_5$ (519,76):				
calculated:	C 46.22%,	H 4.46%,	N 2.69%,	Cl 6.82%;
found:	C 45.92%,	H 4.45%,	N 2.73%,	Cl 6.77%.

Method b)

[0041] A mixture of 11 g (26 millimoles) of ethyl-4-[2'-(iodo)-ethoxy]-2-[2''-(chloro)-benzylidene]-acetoacetate (XIV), 2.99 g (26 millimoles) of methyl-3-(amino)-crotonate (VII) and 110 ml of isopropanol is heated to boiling for 8 hours. The reaction mixture is evaporated, the residue crystallized from cold isopropanol, filtered and washed with cold isopropanol. The crude product is recrystallized from isopropanol. Thus 2.97 g of the desired compound are obtained, yield 22%, mp.: 152 to 155°C.

Example 7

3-[Ethy]-5-[methyl]-2-[2'-(yl)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate]-hexaminium iodide (XI)

[0042] 1.77 g (12.7 millimoles) of hexamethylene tetramine (X) are added to 15 ml of acetonitrile. The mixture is stirred at room temperature for 10 minutes, warmed to 45 to 50°C, whereupon 6.0 g (11,5 millimoles) of 3-[ethyl]-5-[methyl]-2-[2'-(iodo)-ethoxy-methyl]-4-[2''-(chloro)-phenyl]-6-[methyl]-1,4-di-[hydro]-pyridine-3,5-di-[carboxylate] (IX) are added in small portions within about 2 hours. The reaction mixture is stirred at this temperature for 40 hours, allowed to cool to room temperature, filtered and washed successively with acetonitrile and dichloro methane. Thus 6.83 g of the desired product are obtained in the form of a white powder, yield 90%, mp.: 177 to 179°C.

Elementary analysis: for the Formula $C_{26}H_{35}ClIN_5O_5$ (659.957):			
calculated:	C 47.32%	H 3.35%,	N 10.61%;
found:	C 46.84%,	H 5.42%,	N 10.40%.